UAR submission to POST: Technology alternatives to animals in life sciences research

Understanding Animal Research (UAR) is a not-for-profit organisation that explains how animals are used in science. Our 150-plus member organisations are drawn from those who use, fund or require animal research including government agencies, industry, academia, funding bodies, scientific societies, veterinary schools and major medical research charities[1].

New technologies offer researchers new ways to study human and animal biology, with diverse applications from regulatory testing to basic research. A welcome reduction in animal use will be one outcome of researchers phasing-in new technologies, and the new approaches to research that they make possible, but this will not necessarily render animal models obsolete.

For consistency with our prior publications, as well as key historical publications in the scientific literature, we will refer in this document to Non-Animal Technologies (NATs) as a catch-all term, and New Approach Methodologies (NAMs) as those which pertain to regulatory applications.

1. Which technologies show the most promise as alternatives to animal testing in life sciences research?

There is variance within classes of alternatives in terms of their readiness, for instance with organ-chips some organs are easier to model artificially than others. Different sorts of animal use also invite differing levels of complexity, so a technique or set of techniques that is mature enough to replace animals in one area may not be able to replace animals in another. In other cases, new technologies are adding a function we did not have before, for instance for regulatory decisions where there are no relevant animal models[2]. It is thus more helpful to think about phasing-in new methods, if not always as an immediate replacement, then as a complementary and developing technology that may one day form part of a replacement approach.

[1] https://www.understandinganimalresearch.org.uk/about-us/membership-and-funding

[2] Shenton J, Bousnina I, Oropallo M, David R, Weir L, Baker TK, Dunmore HM, Villenave R, McElroy M, Pettersen B, Kokate T, Fuller CL, Homan KA, Hudry E, Wood C, Gunter S. Opportunities and insights from pharmaceutical companies on the current use of new approach methodologies in nonclinical safety assessment. Drug Discov Today. 2025 Apr;30(4):104328. doi: 10.1016/j.drudis.2025.104328. Epub 2025 Mar 12. PMID: 40086787

Below are some examples of promising alternative technologies:

Organ on a chip

"Organ-chips" (or MPS/microphysiological systems) are flexible slides containing tiny tubes lined with human cells that mimic aspects of the physiology of organs (such as lung, liver, or heart) when fluids or gases are passed through them. Organ chips induce normal physiological stresses on cells which in turn respond as if they were in a tissue in an animal. Some have membranes that separate different cell types while still allowing molecular exchange. These can add a new functionality to testing paradigms.

For instance, where animals are used to predict that a compound is safe enough to the liver for the compound to be trialled in a human with 87% accuracy[3], a liver chip can predict toxicity with 87% accuracy[4]. It is therefore measuring a slightly different metric but is nevertheless extremely useful. When used early in a programme of research, it removes compounds that are likely to fail at an earlier point, so preventing further *in vitro,* animal and human tests. These are also being evaluated for regulatory use in the US for identifying Drug Induced Liver Injury (DILI)[5].

The chips can be used both in basic research and drug screening, where they are estimated to be capable of removing 9 out of every 100 drugs that would ultimately fail during preclinical research or clinical trials[6].

There are however limitations. Organ-chips cannot yet capture the full complexity of a whole organism — such as immune system interactions, hormonal regulation, or long-term effects across multiple organs. They require further development and standardisation[7]. If there is even one metric that cannot be modelled artificially, then an animal test will likely still be needed. Some 30% of drugs fail for safety reasons, and 30% of those are liver-related, which means 70% of drugs do not fail for safety reasons, and 70% of the safety concerns are not liver-related[8]. From a technical perspective, all organs are difficult to model, but some throw up more technical challenges than others.

[3] https://pubmed.ncbi.nlm.nih.gov/28893587/
[4] https://www.nature.com/articles/s43856-022-00209-1
[5] https://www.fda.gov/drugs/drug-safety-and-availability/fdas-istand-pilot-program-accepts-submission-first-organ-chip-technology-designed-predict-human-drug
[6] https://www.understandinganimalresearch.org.uk/news/why-do-90-of-new-drugs-fail
[7] Shrimali S, Chen M, Li D, Tong W. New approach methodologies (NAMs) for drug-induced liver injury (DILI): Where are we now? Drug Discov Today. 2025 Sep;30(9):104452. doi: 10.1016/j.drudis.2025.104452. Epub 2025 Aug 11. PMID: 40803573
[8] Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? Acta Pharm Sin B. 2022 Jul;12(7):3049-3062. doi: 10.1016/j.apsb.2022.02.002.

In practical terms, despite the liver having seven major cell types, such as that basic researchers study (compared to a liver chip's four cell types), the liver's main functions from the point of view of pharmaceutical testing (drug metabolism, detoxification, protein synthesis) are dominated by one major cell type: hepatocytes.

This nexus of technological achievability and a strong use-case is one reason liver chips have made the most progress, have been selected for financial backing and have more quickly found an application in drug development. Hepatocytes can be isolated, cultured, and still perform many core functions *in vitro* and the liver has a fairly uniform microarchitecture (lobules), which makes it easier to model than some other organs.

By contrast, the kidney is highly structurally complex: it has multiple distinct compartments (glomeruli, proximal tubules, loop of Henle, distal tubules, collecting ducts) with different specialized cell types. Its function relies on finely tuned osmotic and ionic gradients, and 3D flow dynamics that are difficult to replicate *in vitro*. Filtration (glomerulus) and reabsorption/secretion (tubules) involve mechanical forces and pressure differentials that are currently difficult to recreate in a chip format.

Kidney chips also need much more elaborate microfluidics than the liver chip's simpler perfusion flow, including filtration under pressure (glomerular mimicry), countercurrent exchange mechanisms (loop of Henle) and separate compartments with selective permeability.

Finally, hepatocytes can be obtained relatively easily from human tissue and retain function reasonably well in culture, whereas primary renal epithelial cells lose function quickly in culture. Podocytes (critical for filtration) are especially fragile and difficult to culture long-term.

As with this example, the technology for each organ is at a different level of maturity and in most cases is not yet mature enough to meet the threshold rightly required by regulators.

Non-animal antibodies (e.g. phage display)

Phage display is a molecular biology technique that links a protein's displayed phenotype on the surface of a bacteriophage (a virus that infects bacteria) with its encoding genetic material. This method is used to create and screen vast libraries of proteins, such as peptides and antibodies, to study protein-protein interactions, identify drug candidates, and develop new therapeutics for diseases such as cancer and autoimmune disorders.

It is already widely used in biotech and diagnostics and is both faster and cheaper than animal immunisation, capable of sampling 10^9–10^{11} variants which is far beyond a single animal's repertoire. One can screen directly for affinity (to a degree), specificity, cross-reactivity (or lack of it), pH-dependence, kinetics, and even epitope class and it gives an exact DNA sequence, which is highly reproducible compared to animal antibodies. While phage display performs strongly for diagnostic tasks, it is weaker for developing therapeutic treatments. Its large quantity of proteins can come at the expense of quality since it creates artificial variants that would never be generated by natural B cell diversification: bases can show up too much or not enough in the DNA, so amino acids appear at unnatural spots in the antibody. There can also be issues around how proteins fold and post-translational modifications that occur in eukaryotic cells but not bacteria, plus therapeutics based on phage display have a higher chance of failure[9].

Biomimetic materials (e.g. reconstructed human skin / cornea)

These are already used in place of animal tests for some safety endpoints (e.g. skin irritation, corrosion, ocular toxicity in cosmetics & chemicals) and are accepted by many regulators and harmonisation initiatives such as the OECD and EU REACH in several test guidelines. These are limited to applications where the compound is not intended to penetrate past the skin and they cannot spot the systemic effects of compounds that do.

Numerous compounds such as methanol[10] do not harm skin but once absorbed can cause serious problems within the body, for instance once they are metabolised in the liver or meet parts of the body such as the intestine or brain.

Organoids

These "mini-organs" are used in research and medicine to study disease development, test new drugs for efficacy and toxicity, and develop personalized insights/treatments and cell therapies, reducing the need for animal models.

[9] https://www.understandinganimalresearch.org.uk/application/files/6516/5329/5720/UAR_Antibodies_factsheet_2021.pdf

[10] https://pmc.ncbi.nlm.nih.gov/articles/PMC7394764/

These recreate patient-specific tissues (brain, gut, lung, liver, kidney, retina, pancreas) to study mechanisms that cannot easily be observed in animals such as developmental disorders, fibrosis and neurodegeneration. They can also be used for personalised medicine, drug discovery & safety, infection & host–pathogen work and developmental biology.

Organoids can offer higher throughput than organ on chips, but they are less reliable for systemic safety decisions or adult physiology—unless complemented by vasculature/immune co-cultures and pharmacokinetic (PK) modelling. Many resemble foetal tissue and miss adult metabolism, mechanics, and electrophysiology. There are also more tractable problems such as lack of standardisation.

In silico approaches: *Virtual second species*

This is an example of mining previous animal data to provide an alternative approach to using a new animal in a test. Conceived as a 'CRACK IT' Challenge by the NC3Rs, the aim is to apply advanced computational and mathematical modelling approaches to develop a suite of virtual dog tissues and organs to model toxicological endpoints for New Chemical Entities (NCEs). It seeks to apply advanced *in silico* tools and approaches to support the building of a more robust evidence base to facilitate moving towards using a single (rodent) species in regulatory drug testing, without increasing risk to humans[11]. Utilising the vast amount of historical and contemporary dog study data, a virtual model could be used for the assessment of potential target organ toxicities in the dog. The historical use of the dog for small molecule development has produced considerable data in the literature and study reports that can be exploited.

Omics-based toxicity signatures

This involves the large-scale molecular profiling of cells or tissues (through genomics, transcriptomics, proteomics, metabolomics) combined with computational analysis to understand biological responses to chemicals. They are used in research and some regulatory pilot programs (e.g. ToxCast[12]) and have the potential to identify early biomarkers of damage before symptoms. The current main barriers to their wider use are complexity of interpretation, validation as working for specific applications and the need to better understand how the information could be integrated into regulatory decision making, in order to earn regulatory trust.

[11] https://nc3rs.org.uk/crackit/virtual-second-species
[12] https://www.epa.gov/comptox-tools/toxicity-forecasting-toxcast

2. What are the main challenges/barriers to using these alternative technologies?

There are four main categories:

Scientific & technical readiness
Gaps in validation, transferability and standardisation; insufficient maturity of most assays required to serve the purposes of regulations or the aims of most scientific inquiries; limited throughput or scope for some assays.

Economics & commercial incentives
Public funding not of sufficient scale; significant up-front costs; uncertain return on investment (ROI) for developers/adopters, and access issues (e.g., platforms, data, tissues, IP).[13]

Regulatory & legislative acceptance
Unclear pathways to adoption; uneven international harmonisation, and requirements that still presuppose animal tests in some places[14],[15],[16], [17].

Awareness, confidence & skills
Regulatory systems need to ensure they reflect the increased pace of change[18]; users can lack the in-house skills to use NATs and NAMs or there may be confusion as to how to apply them to real-life scenarios.[19] There may be a need for ongoing training if technologies are frequently reaching maturation having been in development for years, and integration of (sometimes completely) new skillsets to existing workflows may be required.

Contrary to some narratives, there is no lack of political will to 'phase out' animal models. The 3Rs are on the face of UK legislation and progress towards a gradual phase out as technology matures is both one of the manifesto pledges of the current UK government as well as being the international direction of travel.

---

[13] https://nc3rs.org.uk/sites/default/files/2024-03/NC3Rs%20Project%20grants%20scheme%20-%20Applicant%20guidance%20for%20submitting%20a%20full%20application_0.pdf
[14] https://nc3rs.org.uk/news/nams-advisory-group-blog
[15] https://nc3rs.org.uk/sites/default/files/2022-03/2022%20NAMs%20workshop%20-%20Susy%20Brescia%20slides.pdf
[16] https://pmc.ncbi.nlm.nih.gov/articles/PMC10964841/
[17] https://nc3rs.org.uk/sites/default/files/2023-10/NC3Rs%20report%20to%20WHO%20ECBS%20-%20Review%20of%20animal%20testing%20requirements%20in%20WHO%20guidelines%20and%20recommendations%20for%20biologics.pdf
[18] https://nc3rs.org.uk/sites/default/files/2023-02/Rawle%20project%20report.pdf
[19] https://nc3rs.org.uk/who-we-are/our-strategy

Most drivers such as cost, freedom from bureaucracy, practicality and ethics innately discourage the use of animals.

There are instead a wide selection of technical challenges, commercial factors, scientific unknowns and practical issues, for instance whether approaches used in one lab are replicable and/or scalable at a sensible cost or need further refinement to be usable. The US government has, in essence, proposed a scoping exercise through its roadmap to ending animal use[20] that seeks to discover exactly where we are with these technologies and the UK should seek to complement that work and support validation.

Barriers to uptake are not always about lack of awareness of new technology and more about exactly where and how new alternatives can be safely and practically applied for each specific use-case. Medicines regulators, for instance, require a high degree of confidence in any method used to support clinical trials. NAMs must demonstrate that they can inform decisions with equal or greater confidence than traditional approaches to ensure patient safety.

Collaboration and the sharing of data and case studies between regulators themselves, and also the individuals and industries they regulate, will be required to tackle the sheer scale of the task of replacing safety testing systems that evolved over decades as new problems and scenarios were encountered.

The NC3Rs had led several projects that seek to overcome barriers to adoption across numerous sub-applications such as medicines development[21].

The use of NAMs and NATs may be further mediated by Intellectual Property which, although necessary for non-public investment, can potentially restrict who can use the technology and in what way. This may be an unavoidable cost of delivery via commercial and academic routes and the OECD has guidelines for good practice to encourage optimal access[22]. This also occurs with the use of animals, particularly genetically altered strains, although access to these tends to be much less costly to academia than commercial entities.

[20] https://www.fda.gov/media/186092/download?attachment
[21] https://nc3rs.org.uk/news/incorporating-nams-medicines-development-insights-regulators-industry-and-academia
[22] https://www.oecd.org/en/topics/sub-issues/testing-of-chemicals/intellectual-property-elements-in-oecd-test-guidelines.html

What do you think about government policy in this area?

All parts of UK biosciences support the principles of the 3Rs and so we welcome the government's approach and realistic view of the timescales required to be in a position to phase out animal testing. The UK bioscience sector also welcomes the strict regulations that surround the use of animals in science.

When considering specific aspects of animal research, the government commissions advice from the independent Animals in Science Committee[23]. An important principle, therefore, should be for ministers to be reluctant to remove a research method on principle, unless there is very strong evidence, lest we need to call on it to protect man, animals or the environment at some future point. Ministers should resist the urge to prohibit specific techniques or animal species given the likely nature of future threats such as bioweapons and pan/epidemic disease where animals are a transmission vector. The aim instead needs to be to create true alternatives to render the use of animals unnecessary in meeting these challenges.

If you could get policymakers to understand one thing about this area of research, what would it be?

That the 'readiness' of a technology is application-specific. Something that can answer a simple regulatory question might well not be capable of answering a question in fundamental or basic research. For each task, we must ask: Is the alternative mature enough to answer *this particular question* without animals? Can past animal data or human/epidemiological data fill gaps?

Reductions in the use of animals in recent years are thus distributed unevenly across the various ways they are used and we would expect the fastest progress early on as the 'low hanging fruit' of answering simpler questions without using animals is picked.

Regulatory research (12% of animal use in Great Britain in 2023) has seen the greatest falls in the past decade, with reductions of 43%, and basic research (29% of animal use) has seen a fall of around 25% from its 2017 peak before stabilising at around 750,000 procedures a year in Great Britain. Yet the breeding of genetically manipulated animals (45% of animals used) has seen only small annual reductions since its 2013 peak and translational research (14% of animals used) has been stable[24].

[23] https://www.gov.uk/government/organisations/animals-in-science-committee
[24] https://www.gov.uk/government/collections/animals-in-science-statistics